



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16616

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

29 OCT 2005

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2005/000018

International filing date (day/month/year)  
18.01.2005

Priority date (day/month/year)  
29.01.2004

International Patent Classification (IPC) or both national classification and IPC  
C07D209/32, C07D295/08, C07D311/58, C07D311/60, C07D333/64, C07D333/68, A61K31/4025, A61K31/4523,

Applicant  
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000018

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 9 and 10

because:

- ☒ the said international application, or the said claims Nos. 9 and 10 for industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2005/000018

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-11
Inventive step (IS)	Yes: Claims	
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-8,11
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

**see form 210**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 9 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: EP-A-0 791 591 (ELI LILLY AND CO., USA) 27 August 1997)
- D2: MILLER, CHRIS P. ET AL: "Design, Synthesis, and Preclinical Characterization of Novel, Highly Selective Indole Estrogens" JOURNAL OF MEDICINAL CHEMISTRY, 44(11), 1654-1657, 2001, XP001066255
- D3: WO 01/54699 A (ENDORECHERCHE, INC., CAN.) 2 August 2001
- D4: EP-A-1 199 069 (PFIZER PRODUCTS INC., USA) 24 April 2002
- D5: EP-A-1 226 823 (PFIZER PRODUCTS INC., USA) 31 July 2002
- D6: WO 02/03989 A2 (AMERICAN HOME PRODUCTS CORP) 17 January 2002
- D7: WO 01/26651 A2 (ENDORECHERCHE, INC., CAN.) 19 April 2001
- D8: US-B1-6 204 286 (CAMERON KIMBERLY O ET AL) 20 March 2001
- D9: US-A-5 510 357 (PALKOWITZ ET AL) 23 April 1996
- D10: WO 95/10513 A (PFIZER INC; CAMERON, KIMBERLY, O; DA SILVA-JARDINE, PAUL; LARSON, ERIC) 20 April 1995

**1. Novelty of the first invention, Article 33(2) PCT:**

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the indole compounds of claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

In fact the claimed compounds differ from the indole compounds disclosed in D2-D10 on account of the -SO<sub>2</sub>R<sup>11</sup> group ever present in the molecule.

Example 5 of D1 differs from the claimed compounds on account of the alkylsulfonyl substituent on 6-position of the benzo[b]thiophene ring instead of the hydroxyl substituent. **2.**

**Inventive step, Article 33(3) PCT:**

The present application is related to indole compounds that are estrogen receptor (ER) modulators useful in the treatment of gynaecological disorders such as endometriosis and uterine leiomyoma.

All the prior art documents are related to the same technical field.

D1 is considered to be the closest prior art since it discloses generically benzo[b]thiophene derivatives that are ER inhibitors. The structurally closest compound (example 5 of D1) differs from the claimed compounds on account of the presence of a alkylsulfonyl substituent instead of an hydroxyl substituent on the 6-position of the benzo[b]thiophene ring.

The compounds of D3 differ from those claimed on account of the absence of -SO<sub>2</sub>R<sup>11</sup> group either on the indole ring or in the para-position of the phenyl ring. However, in the generic disclosure of indole compounds in claim 20 of D3, the substituents R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>5</sub> can be a moiety that is converted in vivo in hydroxyl. The sulfonic acid or the sulfonamide functionality are among the moieties that are able to be converted in vivo to an hydroxyl group.

The skilled person looking for further ER modulators would from the combination of D1 with D3 arrive in an obvious way to the claimed compounds.

The structural difference between the compounds of D1 and those presently claimed is to be regarded rather as a minimal structural difference so that it is considered that the technical problem of providing further estrogen receptor modulators has been solved in an obvious way, since the retention of biological activity of the present compounds was to be expected in the light of D1.

Hence, the underlying technical problem to be solved by the present invention may be regarded as the provision of ER modulators, which provide an unexpected effect with regard to the compounds of the prior art D1.

Since the present application does not contain any evidence for such surprising effect compared to the already known ER modulators, no inventive step could be acknowledged. Thus, the requirements of Article 33(3) PCT are not considered to be satisfied.

**Re Item VI**

**Certain documents cited**

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004/009086	29.01.2004	16.07.2003	22.07.2002
WO2004/075894	10.09.2004	21.01.2004	25.02.2003

These documents are related to 1-(4-(2-piperidinylethoxy)phenoxy)-2-(4-methanesulfonylphenyl)-6-hydroxynaphthalenes and 1-(3-(2-piperidinylethoxy)phenoxy)-2-(4-methanesulfonylphenyl)-6-hydroxybenzothiophenes as ER modulators.

**Re Item VIII**

**Certain observations on the international application**

The present application does not meet the requirements of Article 6 PCT in that the matter for which protection is not supported by the description (Article 5 PCT):

The description does not disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a skilled person. Due to the fact that there is no single example illustrating the claimed compounds, a lack of disclosure within the meaning of Art. 5 PCT arises.